NIH RELAIS Document Delivery

NIH-10289407

JEFFDUYN

NIH -- W1 MA34H

JOZEF DUYN
10 Center Dirve
Bldg. 10/Rm.1L07
Bethesda, MD 20892-1150

ATTN:
PHONE: 301-594-7305
FAX: -
E-MAIL:

SUBMITTED: 2002-09-04 08:27:56
PRINTED: 2002-09-05 14:43:01
REQUEST NO.:NIH-10289407
SENT VIA: LOAN DOC
7999124

NIH Fiche to Paper Journal

TITLE: MAGNETIC RESONANCE IMAGING
PUBLISHER/PLACE: Pergamon, New York :
VOLUME/ISSUE/PAGES:1994;12(4):661-7 661-7
DATE: 1994
AUTHOR OF ARTICLE: Husted CA; Duijn JH; Matson GB; Maudsley AA; Weiner MW
TITLE OF ARTICLE: Molar quantitation of in vivo proton metabolites i
ISSN: 0730-725X
OTHER NOS/LETTERS: Library reports holding volume or year
8214883
8057771
SOURCE: PubMed
CALL NUMBER: W1 MA34H
REQUESTER INFO: JEFFDUYN
DELIVERY: E-mail: jhd@helix.nih.gov
REPLY: Mail:

Pergamon

Magnetic Resonance Imaging, Vol. 12, No. 4, pp. 661–667, 1994

0730-725X/94 $6.00 + .00

0730-725X(93)E0062-S

● *Original Contribution*

MOLAR QUANTITATION OF IN VIVO PROTON METABOLITES IN HUMAN BRAIN WITH 3D MAGNETIC RESONANCE SPECTROSCOPIC IMAGING

C.A. HUSTED, J.H. DUIJN,* G.B. MATSON, A.A. MAUDSLEY, AND M.W. WEINER

Magnetic Resonance Unit, Department of Veterans Affairs Medical Center, and Departments of Medicine, Radiology and Pharmaceutical Chemistry, University of California, San Francisco, CA 94121, USA

A method for molar quantitation of in vivo proton metabolites in human brain with three-dimensional (3D) proton magnetic resonance spectroscopic imaging (MRSI) is described. The method relies on comparison of brain and calibration phantom measurements, with corrections for coil loading, and spin-lattice and spin-spin relaxation times. A 3D proton MRSI pulse sequence was developed which acquires two echoes and enables acquisition of both the TMS coil loading reference phantom and proton metabolite signals from a single experiment. With the aqueous fraction (tissue water) taken into account, the calculated molar concentrations from 24 centrum semiovale white matter voxels from 4 control subjects were (mmol/l ± SD): N-acetyl aspartate = 14.6 ± 2.8, total creatine+phosphocreatine = 6.0 ± 1.2, total choline = 1.9 ± 0.4. These values are equivalent to previously reported results obtained from single volume localized proton magnetic resonance spectroscopy.

Keywords: **Magnetic resonance spectroscopic imaging; Proton spectroscopy; Quantitation; Brain.**

INTRODUCTION

Quantitative proton (^{1}H) NMR spectroscopy provides essential information for the understanding of the physiology of neurons, energy metabolism, and lipid metabolism in living systems. The ability to determine absolute concentrations eliminates the assumptions made, especially concerning metabolite changes in disease processes, when metabolite ratios are used. There have been several reports of proton molar quantitation from 8–27 cc single volumes of human brain.[1–10] These reports utilized either water[2,3,9] or creatine[7] as an internal standard, or external reference phantoms.[1,4–6,8]

The goal of these experiments was to determine absolute proton metabolite concentrations from multiple voxel magnetic resonance spectroscopic imaging (MRSI) data using an external lactate calibration phantom. This was accomplished by implementing a 3D MRSI technique[11,12] which acquires two echoes and enables acquisition of both a TMS coil loading reference phantom and proton in vivo metabolite signals from a single experiment.[13] This procedure enables acquisition and quantitation of multiple small (1.3 cc) volumes throughout the majority of the brain from a single MRSI experiment.

METHODS

Instrumentation and Acquisition

Studies were conducted with a Philips Gyroscan S15 whole body imaging/spectroscopy system operating at 2.0 Tesla. A proton imaging saddle-type head coil was used for MRI and MRSI. The method used to calculate absolute metabolite concentrations is analogous to the methods previously used for quantitation of ^{31}P magnetic resonance spectroscopy (MRS) and MRSI metabolites,[14,15] and relies on the use of two reference phantoms: 1) a large lactate calibration phantom of known concentration, and 2) a 3 cc tetramethylsilane (TMS) coil loading reference phantom to correct for pulse lengths and coil loading differences between the subject and the lactate calibration phantom.

Three-dimensional ^{1}H MRSI data was acquired with PRESS volume preselection[16] used in combina-

RECEIVED 4/1/93; ACCEPTED 10/18/93.
Address correspondence to Cynthia Husted, PhD, Magnetic Resonance Unit (11M), DVA Medical Center, 4150 Clement St., San Francisco, CA 94121.

*Current address: In vivo NMR Research Center, National Institutes of Health, Bethesda, MD.

tion with double WEFT water suppression, as previously described.[17] The one important modification made to the previously reported 3D MRSI experiment[17] was acquisition of both first and second echoes of the PRESS sequence (Fig. 1) to measure both the TMS coil loading reference phantom (acquired with the first echo) and metabolite signals (acquired with the second echo) in a single experiment. The TMS coil loading reference phantom was fixed in a position just beyond the head of the subject, as indicated in Fig. 2. As shown in Figs. 1 and 2, the first echo contained signal from a column which included the TMS coil loading reference phantom, and the second echo contained metabolite signals from the volume of interest (VOI). This particular experimental setup has the advantage that the TMS and metabolite signals of the subject and lactate calibration phantom are affected by signal losses during the first two slice selections in a similar manner. Careful adjustment of the pulse angle was made to ensure that the pulse angle at the reference vial was the same in both phantom and subject experiments. The TMS sample was spatially localized away from the brain signals by the MRSI experiment, so the total TMS signal could be obtained without contamination by integrating over all voxels containing significant TMS signal. For the lactate calibration phantom and brain studies, the voxels were selected away from edges so that any "bleeding" which occurred from adjacent voxels was presumably from homogeneous tissue and had a metabolite concentration which was of the same concentration as the selected voxel.

Three-dimensional MRSI spectral data and coil loading reference data (the TMS signal) were acquired from a single experiment for separate studies of the lactate calibration phantom and the human subjects. Spectral data from the lactate calibration phantom was selected from the same region in the coil as the human spectral data to compensate for the effects of coil inhomogeneities. Use of the TMS coil loading reference phantom as a concentration reference would not provide compensation for the inhomogeneities in the saddle-type coil used.

Four normal adult human subjects (3 females, 1 male) were studied, and two studies on a lactate calibration phantom (20 mM lactate in 3% gelatin matrix) were performed. Transverse and sagittal MR images were taken for each study. The transverse images were acquired with an angulation corresponding roughly to

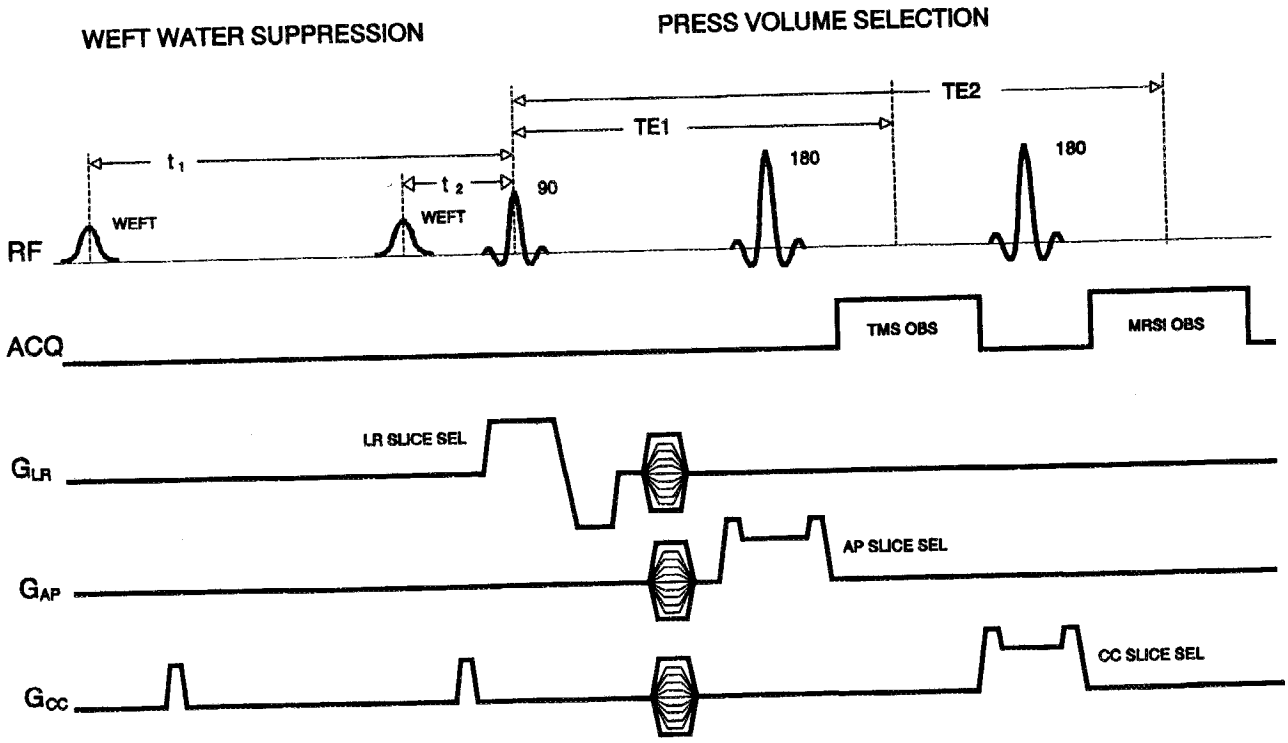
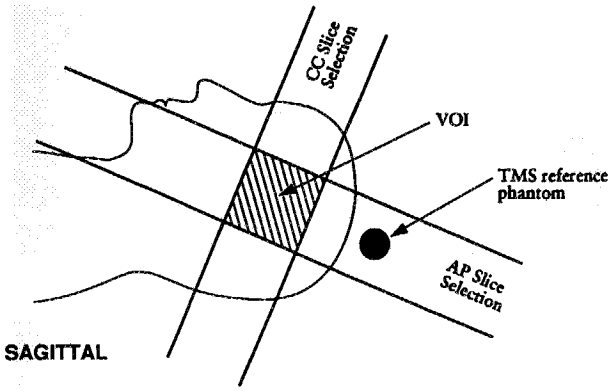
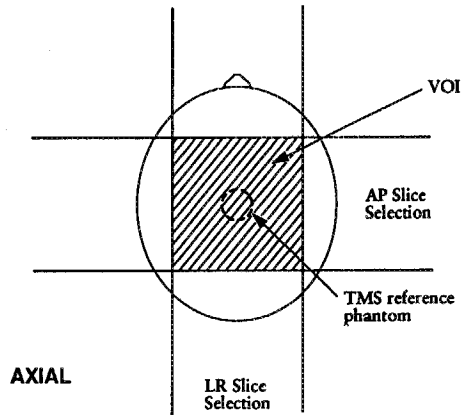


Fig. 1. Acquisition scheme of 3D ^{1}H MRSI experiment with double echo acquisition. The first part of the pulse sequence consists of a double WEFT water suppression sequence. The second part contains the PRESS sequence for selection of the VOI, together with three phase-encoding gradients. TE1 refers to acquisition of the first echo containing the TMS coil loading reference phantom signal and TE2 the second echo containing the proton MRSI metabolite signals.



(A)



(B)

Fig. 2. Schematic representation of volume selection for first and second echoes. (A) illustrates (1) the detection of the TMS coil loading reference phantom with the AP (anterior–posterior) slice selective gradient, and (2) the sagittal view of the MRSI VOI selection with both the CC (caudal–cranial) and AP slice selective gradients. (B) illustrates an axial view of the selection of the MRSI VOI with both the LR (left–right) and AP slice selective gradients.

the orbital-auditory meatus plane. Nonlocalized shimming was performed following acquisition of the MRI data. This was followed by gradient tuning,[16] localized shimming (over an area ~15% larger than the VOI in all 3 directions), and optimization of water suppression. The 3D ^{1}H MRSI experiments were performed using 16 × 16 × 12 phase-encoding steps over a 140 mm × 140 mm × 136 mm field of view. A spherical k-space sampling scheme was used which roughly halved the number of k-space points sampled.[18] Other parameters were: TE1 = 116 ms (TMS signal acquisition); TE2 = 272 ms (metabolite signal acquisition); TR = 2000 ms; 1 average; measurement time = 44 min. The effective voxel size, computed from the full width at half height of the point spread function and corrected for the effects of spherical k-space sampling and spatial filtering, was 1.3 cc.

Data Processing

The MRSI data were processed on a VAX workstation using 4D Fourier transform reconstruction with 1.0 Hz exponential filtering in the frequency domain and mild spatial filtering.[18] The MRSI data were zero-filled in both frequency and spatial dimensions before a 4D Fourier transform was applied. After the final reconstruction, one MRSI plane corresponded to one MRI plane. Spectroscopic image display software[18] was used to display MR images, MRS images, and spectra (Figs. 3, 4).

Metabolite images were generated by spectral integration of N-acetyl aspartate (NAA), total choline (Cho) and total creatine+phosphocreatine (Cr+PCr) during reconstruction. The spectroscopic image display software provided registration of the MR images with the MRS images so that the cursor locations registered simultaneously on both images. Using the MR image as a guide, single voxel spectra were chosen from posterior frontal and parietal centrum semiovale white matter in the human subject and from corresponding regions in the phantom. Gross contamination of voxels by CSF was avoided by choosing voxels for analysis well removed from ventricles and sulci. Magnitude spectra were used to avoid phase distortions. Spectra were fit to Gaussian lineshapes and integrated using commercially available software (Tripos Associates, Inc., St. Louis, MO). Metabolite concentrations are given as mean ± standard deviation (SD).

Quantitation of Metabolites

Molar concentrations were calculated using an extension of methods previously employed.[10,14,15] Identical volumes were used for human subject and calibration phantom experiments. Molar concentrations for each metabolite in the chosen volumes were calculated by:

$$[\text{metabolite}]_S = [\text{lactate}]_P * \frac{AF_P}{AF_S} * \frac{S_P}{S_S} * \frac{R_P}{R_S} * \frac{I_S}{I_P} * \frac{I_{\text{TMS},P}}{I_{\text{TMS},S}} * \frac{N_{H,P}}{N_{H,S}} \quad (1)$$

where

$[\text{metabolite}]_S$ = molar concentration of metabolite, subject

$[\text{lactate}]_P$ = molar concentration of lactate phantom = 20 mM

AF_P = aqueous fraction, phantom = 0.97

AF_S = aqueous fraction, subject = 0.72 (for white matter[14])

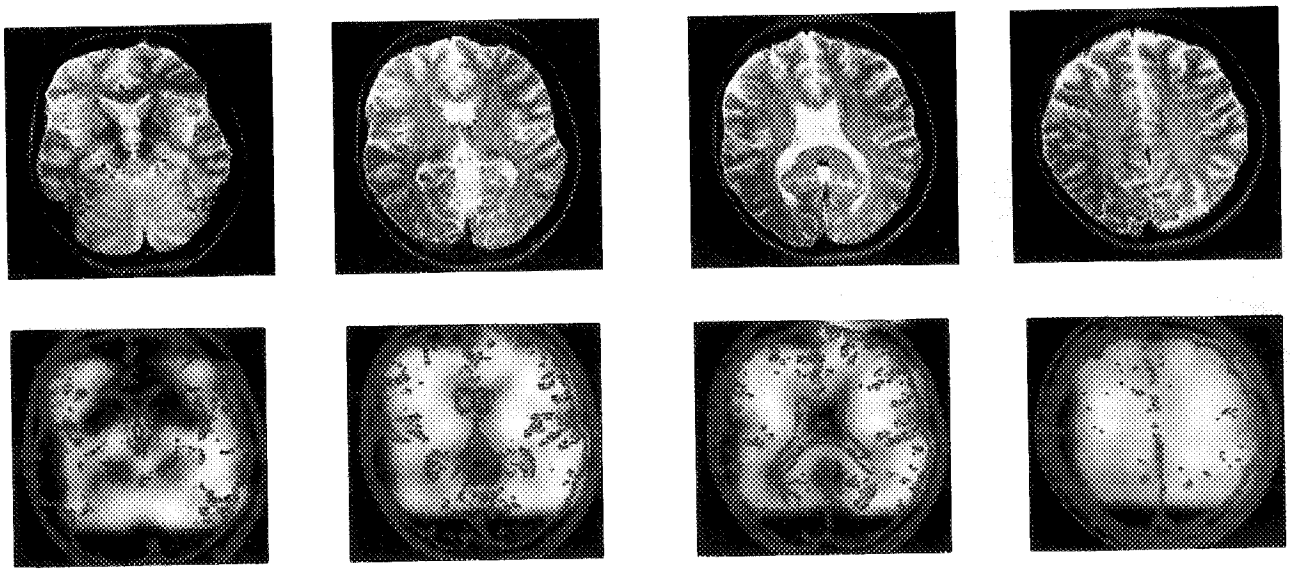


Fig. 3. Multiplane 3D ^{1}H MRSI NAA images of normal human subject with highpass filter of MRI overlaid in red. Corresponding T_2-weighted (angulated) magnetic resonance images are shown. The MRIs and spectral images are (left to right) inferior to superior through the brain.

S_P, S_S = saturation corrections, calibration phantom and subject

R_P, R_S = spin echo corrections, calibration phantom and subject

I_S = integral of metabolite, subject

I_P = integral of lactate calibration, phantom

$I_{TMS,P}, I_{TMS,S}$ = integrals of TMS coil loading reference phantom, acquired with lactate calibration phantom ($I_{TMS,P}$) and human subject ($I_{TMS,S}$)

$N_{H,P}, N_{H,S}$ = correction for number of protons per molecule, phantom and subject.

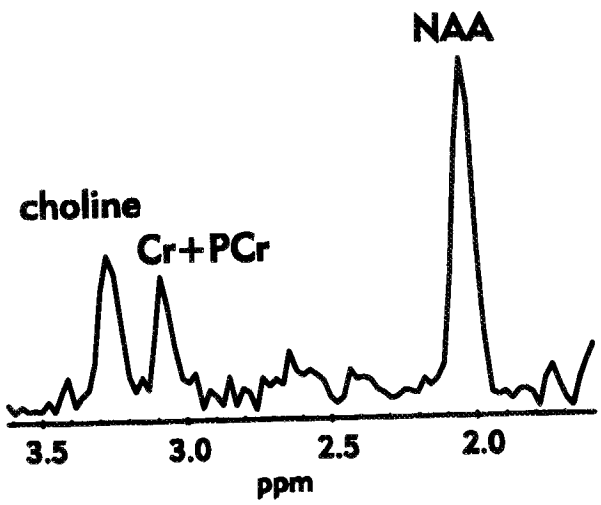


Fig. 4. Single voxel proton MRSI spectrum selected from region of centrum semiovale. Spectral assignments are as indicated.

The saturation correction was

$$S = \frac{\sin\alpha\left[1 - \exp\left(\frac{-TR}{T_1}\right)\right]}{(1 - \cos\alpha)\left[\exp\left(\frac{-TR}{T_1}\right)\right]} \quad (2)$$

where

α = tip angle (90° for these experiments)

TR = repetition time

T_1 = spin-lattice relaxation time.

The spin-echo correction was

$$R = \exp\left(\frac{-TE}{T_2}\right) \quad (3)$$

where

TE = echo time

T_2 = spin-spin relaxation time.

Published human brain T_1 and T_2 values obtained at 1.5 T were used for the MRSI metabolites.[7] Proton T_1 relaxation times for NAA, Cr, and Cho obtained at 2.0 T from 17 control subjects are comparable to those reported at 1.5 T (J. Frahm, private communication). Thus, the T_1 and T_2 relaxation times reported at 1.5 T[7]

Table 1. T_1 and T_2 values used in calculations of molar concentrations

Metabolite	T_1 (s)	T_2 (ms)
NAA	1.5[a]	370[a]
Cr+PCr	1.6[a]	230[a]
Cho	1.2[a]	340[a]
lactate	0.83[b]	315[b]

[a] T_1, T_2 human subject values.[7]
[b] T_1, T_2 phantom values obtained experimentally from one phantom study.

were used in this study. Phantom lactate T_1 and T_2 values were determined experimentally from 4 different inversion recovery times or 4 different TE times. Relaxation calculations were fit using commercially available software (Tripos Associates, Inc., St. Louis, MO). We believe that the dominant error in the concentrations is due to the curve fitting of the metabolite peaks in the presence of noise. Thus, the measured standard deviations should be reasonably accurate. The other potentially important source of error is in the estimates of T_1 and T_2. The calculation of how errors in these relaxation times affect concentrations is straightforward, and the equations are included in the Appendix.

RESULTS AND DISCUSSION

Figure 3 shows multi-plane NAA spectroscopic images and corresponding magnetic resonance images. Figure 4 shows a single voxel spectrum extracted from the centrum semiovale white matter. The three peaks represent, from left to right, total Cho, total Cr+PCr, and NAA. The signal-to-noise of this spectrum was approximately 12:1 for NAA.

The MRSI concentration estimates were obtained by Eq. (1) with the use of the T_1 and T_2 values given in Table 1. The calculated mM values, corrected for aqueous fraction, from a total of 24 centrum semiovale white matter spectra from four control subjects were (mean ± SD): NAA = 14.6 ± 2.8 mM, Cr+PCr = 6.0 ± 1.2 mM, and Cho = 1.9 ± 0.4 mM. The aqueous fraction correction accounts for the white matter water concentration, and in this study it was assumed to be 72% that of pure water.[14] Thus, $AF_P/AF_S = 1.35$. When omitting this correction, the calculated metabolite molar MRSI values are (Table 2): NAA = 10.9 ± 2.0 mM, Cr+PCr = 4.5 ± 1.2 mM, and Cho = 1.4 ± 0.4 mM. The above values, in comparison with previously reported single volume concentrations, are given in Table 2. To facilitate comparison of concentration units across laboratories, reported results were converted as necessary to present all values in Table 2 in mM units corrected for aqueous fraction. The MRSI concentration values are in the range of values recently reported by others, providing evidence for the validity of this quantitation method. The advantage of this technique is that data from multiple small volumes throughout the brain are acquired from one experiment. Furthermore, in this experiment the TMS coil loading reference phantom is spatially localized away from tissue, eliminating potential spectral contamination from tissue water or lipid. The smaller volumes of the MRSI experiment, and thus greater tissue homogeneity within the volumes, may account for some of the differences with previously reported results. Gray-

Table 2. 3D proton MRSI quantitation results of brain white matter in comparison to recently reported single volume MRS white matter data, expressed in units of mmol/l.[1-6]

Reported value	No. subjects/No. regions	NAA	Cr+PCr	Cho
3D MRSI corrected for AF*	4/24	14.6 ± 2.8	6.0 ± 1.2	1.9 ± 0.4
3D MRSI not corrected for AF*	4/24	10.9 ± 2.0	4.5 ± 1.2	1.4 ± 0.4
ref. (1)†	26/41	12.2 ± 1.0	8.5 ± 0.8	2.5 ± 0.3
ref. (2)	5/15	11.6 ± 1.3	7.6 ± 1.4	1.7 ± 0.5
ref. (3)‡	10/10	17.3 ± 2.3	11.0 ± 1.3	2.0 ± 0.5
ref. (4)†	21/21	11.7 ± 1.6	7.8 ± 1.8	2.1 ± 0.7
ref. (5)‡	10/10	9.2 ± 0.2	6.6 ± 0.1	1.6 ± 0.0
ref. (6)†,‡	18/18	14.3 ± 2.8	11.3 ± 1.5	3.1 ± 0.7

Values are reported as mean ± standard deviation, mmol/l units corrected for aqueous fraction (white matter water concentration). *AF, aqueous fraction. †External reference quantitation method in which reported values were not corrected for aqueous fraction, and thus were corrected here for aqueous fraction by dividing metabolite concentration by 0.72 (white matter water concentration assumed to be 72% that of pure water). ‡Literature values reported in mmol/kg wet weight units were converted to mmol/l using the specific gravity of brain tissue (ρ = 1.04 kg/l) as the conversion factor.[1]

white matter differences have been noted by magnetic resonance spectroscopy[5] and would presumably be more pronounced with homogeneous tissue types.

A few limitations of the current MRSI experiment must be addressed. Although T_1 and T_2 corrections were made in the molar calculations, the relaxation times used were those previously reported at 1.5 Tesla and from large (27–64 cc) volumes. A more thorough 3D MRSI analysis would include T_1 and T_2 measurements at 2.0 Tesla and from smaller volumes. RF inhomogeneities in the saddle-type coil may be improved with a birdcage resonator.[19] The assumption of constant aqueous fraction has potential difficulties. Changes in tissue water content occur in a wide variety of pathologic conditions which produce brain edema including tumor, ischemia, inflammation, and electrolyte disorders. Furthermore, brain edema may be due to increased extracellular water (which does not affect intracellular metabolite concentrations) while in other cases it is due to increased intracellular water (which does affect intracellular metabolite concentrations). The 3D proton MRSI quantitation technique described in this technical note enables acquisition of quantitative data from multiple volumes in the brain simultaneously, and provides results that are similar to those obtained using single volume magnetic resonance spectroscopy.

Acknowledgments—This project was supported by a National Multiple Sclerosis Society Postdoctoral Fellowship (CAH), National Institutes of Health PHS grants RO1-CA48815, RO1-DK33293, and HL07192, the Department of Veterans Affairs Research Service, and Philips Medical Systems.

APPENDIX

The use of an incorrect relaxation time T_1 in the saturation correction, S, alters the saturation correction according to:

$$\delta S/S = [(\mathrm{TR}/T_1) * \exp(-\mathrm{TR}/T_1) * (\cos(\alpha) - 1)]/ [(1 - \cos(\alpha) * \exp(-\mathrm{TR}/T_1)) * (1 - \exp(-\mathrm{TR}/T_1))] * \delta T_1/T_1$$

where δS is the change in the saturation correction and $\delta T_1 = (\delta T_1 \text{ correct} - \delta T_1)$ used in the calculation of S.

The use of an incorrect relaxation time T_2 in the spin-echo correction, R, alters the spin-echo correction according to:

$$\delta R/R = (\mathrm{TE}/T_2) * \delta T_2/T_2$$

where δR is the change in the saturation correction and $\delta T_2 = (\delta T_2 \text{ correct} - \delta T_2)$ used in the calculation of R.

REFERENCES

1. Michaelis, T.; Merboldt, K.-D.; Bruhn, H.; Hanicke, W.; Math, D.; Frahm, J. Absolute concentrations of metabolites in the adult human brain in vivo: quantification of localized proton MR spectra. *Radiology* 187:219–227; 1993.
2. Christiansen, P.; Henriksen, O.; Stubgaard, M.; Gideon, P.; Larsson, H.B.W. In vivo quantification of brain metabolites by 1H-MRS using water as an internal standard. *Magn. Reson. Imag.* 11:107–118; 1993.
3. Barker, P.B.; Soher, B.J.; Blackband, S.J.; Chatham, J.C.; Mathews, V.P.; Bryan, R.N. Quantification of proton NMR spectra of the human brain using tissue water as an internal concentration reference. *NMR Biomed.* 6:89–94; 1993.
4. Hennig, J.; Pfister, H.; Ernst, T.; Ott, D. Direct absolute quantification of metabolites in the human brain with In vivo localized proton spectroscopy. *NMR Biomed.* 5: 193–199; 1992.
5. Kreis, R.; Ernst, T.; Ross, B.D. Absolute quantitation of water and metabolites in the human brain. II. Metabolite concentrations. *J. Magn. Reson.*, Series B, 102:9–19; 1993.
6. Narayana, P.A.; Johnston, D.; Flamig, D.P. In vivo proton magnetic resonance spectroscopy studies of human brain. *Magn. Reson. Imag.* 9:303–308; 1991.
7. Frahm, J.; Bruhn, H.; Gyngell, M.L.; Merboldt, K.D.; Hanicke, W.; Sauter, R. Localized proton NMR spectroscopy in different regions of the human brain in vivo. Relaxation times and concentrations of cerebral metabolites. *Magn. Res. Med.* 11:47; 1989.
8. Narayana, P.A.; Fotedar, L.K.; Jackson, E.F.; Bohan, T.P.; Butler, I.J.; Wolinsky, J.S. Regional in vivo proton magnetic resonance spectroscopy of brain. *J. Magn. Reson.* 83:44–52; 1989.
9. Thulborn, K.R.; Ackerman, J.J.H. Absolute molar concentrations by NMR in inhomogeneous B1. A scheme for analysis of in vivo metabolites. *J. Magn. Reson.* 55:357–371; 1983.
10. Tofts, P.S.; Wray, S. A critical assessment of methods of measuring metabolite concentrations by NMR spectroscopy. *NMR Biomed.* 1:1–10; 1988.
11. Brown, T.R.; Kincaid, B.M.; Ugurbil, K. NMR chemical shift imaging in three dimensions. *Proc. Natl. Acad. Sci. USA* 79:3523–3526; 1982.
12. Maudsley, A.A.; Hilal, S.K.; Perman, W.H.; Simon, H.E. Spatially resolved high resolution spectroscopy by "four dimensional" NMR. *J. Magn. Reson.* 51:147–152; 1983.
13. Duijn, J.H.; Husted, C.A.; Matson, G.B.; Maudsley, A.A.; Weiner, M.W. Molar quantitation of in vivo proton metabolites in human brain with 3D MR spectroscopic imaging [abstract]. *Society of Magnetic Resonance in Medicine* 2:3807; 1992.
14. Hubesch, B.; Sappey-Marinier, D.; Roth, K.; Meyerhoff, D.J.; Matson, G.B.; Weiner, M.W. P-31 MR spectroscopy of normal human brain and brain tumors. *Radiology* 174:401–409; 1990.

15. Lara, R.S.; Matson, G.B.; Hugg, J.W.; Maudsley, A.A.; Weiner, M.W. Quantitation of in vivo phosphorus metabolites in human brain with magnetic resonance spectroscopic imaging (MRSI). *Magn. Reson. Imag.* 11(2): 273–278; 1993.
16. Luyten, P.R.; Marien, A.J.H.; den Hollander, J.H. Acquisition and quantitation in proton spectroscopy. *NMR Biomed.* 4:64–69; 1991.
17. Duijn, J.H.; Matson, G.B.; Maudsley, A.A.; Weiner, M.W. 3D phase-encoding 1H spectroscopic imaging of human brain. *Magn. Reson. Imag.* 10:315–319; 1992.
18. Maudsley, A.A.; Lin, E.; Weiner, M.W. Spectroscopic imaging display and analysis. *Magn. Reson. Imag.* 10: 471–485; 1992.
19. Hayes, C.E.; Edelstein, W.A.; Schenck, J.F.; Mueller, O.M.; Eash, M. An efficient, highly homogeneous radiofrequency coil for whole-body NMR imaging at 1.5 T. *J. Magn. Reson.* 63:622–628; 1985.